Journal of Neuro-Oncology 6: 29–30 (1988)

Severe encephalopathy associated with ifosfamide administration in two children with metastatic tumors

Maria A. Gieron, Larry S. Barak and Jaime Estrada
Department of Pediatrics, University of South Florida, Tampa, Florida, USA

Key words: ifosfamide, encephalopathy

Summary

We studied two children with recurrent cancer, who during treatment with ifosfamide developed severe encephalopathy characterized by coma of several days duration. Ifosfamide was used as a single drug without mesna as an uroprotector. A 1-hour infusion of ifosfamide (1.8 g/m^2) was given on days one and two of a planned 5-day course. Encephalopathy was associated with severe electroencephalographic abnormalities, e.g. slowing in delta range in one patient and electrographic seizures in another. Both, clinical and electroencephalographic features of encephalopathy were reversible.

Introduction

Ifosfamide (IF) is an oxazaphosphorine alkylating agent, structurally an isomer of the extensively used anti-cancer drug cyclophosphamide. Only recently IF has been considered in treatment of pediatric tumors either in combination with other drugs or as a single agent [1–3]. DeKraker and Voute [1] reported 1 case of seizure among 24 children treated with IF/mesna in combination with vincristine. In Pinkerton's *et al.* [2] group of 21 children treated with IF/mesna, 2 developed transient neurologic deficit; 1 of 2 had a 5 min lasting convulsions while another one had facial spasms and trismus. Pratt *et al.* [3] reported the neurologic toxicity of IF in 11 of 50 patients with pediatric malignant solid tumors. All affected patients had some mental status changes but only one patient was comatose. All disturbances of mental status returned to normal within 3 days after cessation of IF/mesna.

We studied two children with recurrent cancer, who during treatment with IF developed severe encephalopathy characterized by coma of several days duration in both patients and seizures in one.

Case reports

Our first patient (C.B.), a 4-year-old white male had metastatic Wilms tumor. He failed prior chemotherapy and radiation therapy. The second patient (N.A.) was a 4½-year-old white female with metastatic neuroblastoma. She also failed chemotherapy, surgery and radiation therapy. IF was used without mesna. In both cases a 1-hour infusion of IF (1.8 g/m^2) was given on days 1 and 2 of a planned 5-day course. Additional medications included ampicillin, allopurinol, acetazolamide, meperidine, and promethazine in C.B. and none in N.A. Twelve hours after the second IF dose, C.B. became comatose with intermittent opisthotonic posturing and a disconjugate gaze. Treatment with anticonvulsants, diphenhydramine, and naloxone did not cause any change in patient's condition. His symptoms slowly abated over the next 5 days. N.A. became comatose 4 hours after the second IF dose. She had intermittent twitching of the arms and legs along with myoclonic jerks lasting over 24–36 hours. In addition she had seizures characterized by vomiting, loss of muscle tone and upward eye devia-

tion for periods lasting a few seconds to a minute. She was treated with phenytoin. Over the next 7 days her mental status returned to normal and seizure frequency declined. Both patients had normal serum electrolytes, calcium, magnesium, glucose, and liver function tests at the initiation of and during the treatment with IF. A head computerized tomographic scan done after the onset of encephalopathy was normal in both patients.

Electroencephalograms (EEGs) were abnormal in both patients during the encephalopathy. There was a continuous 1–2 Hz delta activity in C.B. on day 2 of the neurotoxicity, and 2–3 Hz spike-and-wave discharges changing in amplitude and frequency consistent with electrographic seizure in N.A. on day 1 of the neurotoxicity. Gradual reversal of EEG abnormalities was observed during the course of encephalopathy and it was associated with improvement in the patients' mental and seizure status.

Discussion

Twenty-five courses of either IF alone or IF/mesna therapy were delivered to 6 patients in our center to date. The dose of IF was the same (1.8 g/m^2) in all courses. Two of 25 courses (8%) were followed by development of severe neurotoxicity. In 16 of 25 courses including those received by our 2 patients who developed neurotoxicity, IF was used as a single agent since mesna was not available at that time. Mesna was considered in the past as an agent possibly contributing to development of IF neurotoxicity [4]. Addition of mesna into 9 courses of IF therapy in other patients did not make any difference. These facts support an opinion that mesna has no essential role in the development of such toxicity. We could also not attribute neurotoxicity in our patients to narcotics or antiemetics since one patient received none and the patient who received some did not improve after naloxone and diphenhydramine administration. The clinical course in our cases underlines the seriousness of the IF neurotoxicity. Encephalopathy in our patients was more severe and longer lasting than in other reported similarly treated pediatric patients [1–3]. We believe that IF or its toxic metabolites were responsible for the neurologic toxicity in our patients.

Pratt *et al.* [3] found that the EEG abnormalities can occur in both symptomatic and nonsymptomatic patients treated with IF. The authors concluded that the EEG was neither a sensitive nor specific method of monitoring for IF/mesna neurotoxicity. However, serial EEG performed in our symptomatic patients showed that severity of EEG changes correlated well with an actual clinical status. Therefore, EEG may be of value as one of the objective indicators of the improvement.

References

1. DeKraker J, Voute PA: Ifosfamide, mesna and vincristine in paediatric oncology. Cancer Treat Rev 10 (Suppl A):165–166, 1983
2. Pinkerton CR, Rogers H, James C, Bowmam A, Barbor PRH, Eden OB, Pritchard J: A phase II study of Ifosfamide in children with recurrent solid tumours. Cancer Chemother Pharmacol 15:258–262, 1985
3. Pratt CB, Green AA, Horowitz ME, Meyer WH, Etcubanas E, Douglass E, Hayes FA, Thompson E, Wilimas J, Igarashi M, Kovnar E: Central Nervous System CNS toxicity following Ifosfamide (Ifos) treatment for children with malignant solid tumors. J Clin Oncol 4:1253–1261, 1986
4. Cantwell BMJ, Harris AI: Ifosfamide/Mesna and encephalopathy. Lancet 1: 752, 1985 (letter)

Address for offprints: Maria A. Gieron, Department of Pediatrics, 1 Davis Blvd., Suite 408, Tampa, Florida 33606, USA